State of the Art

Noninvasive Assessment of Blood Gases[1-3]

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Introduction

In the past 30 yr rapid technologic advances have permitted noninvasive devices for assessment of blood gases to be moved from the investigational laboratory setting to the patient's bedside, where they are being increasingly applied by clinicians to evaluate and monitor patients with cardiopulmonary disorders. Coincident with these technologic developments the realization has become widespread that blood gases change from moment to moment when patients exercise, sleep, or receive anesthesia. The problems of monitoring the rapidly changing oxygenation and ventilation of acute and chronically ill patients by intermittent arterial blood gas measurement have given additional impetus to the development and application of noninvasive devices for patient care. In particular, the introduction of pulse oximetry made clinicians more aware of noninvasive devices for blood gas monitoring of patients both in the hospital and office settings. This review presents the current state of the art of noninvasive devices that are available for clinical monitoring of oxygen and carbon dioxide in neonates, children, and adults and presents clinical and technical requirements for appropriate application of these devices.

Clinical Applications and Technical Requirements

Critical Care Applications

Obtaining blood for Pa_{O_2} determination is easily accomplished in the adult in the critical care setting, where indwelling arterial catheters have become commonplace, thereby minimizing patient distress caused by repeated arterial puncture. This ease of sampling, however, may lead to significant blood loss and this, together with the high cost of repetitive blood gas analyses and the repeated exposure to potentially biologically hazardous blood, may suggest the desirability of identifynig alternative methods besides *in vitro* blood gas analysis for monitoring oxygen delivery. Moreover, in infants obtaining frequent blood samples for Pa_{O_2} monitoring may prove difficult when the umbilical artery is not available as a sampling site, and blood loss from *in vitro* blood gas analysis may be a particular concern in the neonate.

The development of devices for assuring Sa_{O_2} such as the oximeter offers ready access to Sa_{O_2} data. However, the use of the oximeter presents the clinician with the challenge of determining the Pa_{O_2} when the oxygen dissociation curve is not well defined. Because of the shape and variability of the oxyhemoglobin dissociation curve in critically-ill adults, infants, and children, a given Sa_{O_2} is compatible with a range of arterial oxygen tensions. Moreover, the range of Pa_{O_2} uncertainty is further increased when a pulse oximeter with an assumed accuracy of $\pm 2\%$ is used to determine Sa_{O_2}. The range of predicted Pa_{O_2} values that correspond to oximetrically determined Sa_{O_2} is important to the neonatalogist who is attempting to adjust the inspired oxygen and ventilator settings so that hypoxemia ($<$ 50 to 60 mm Hg) and hyperoxemia ($>$ 100 mm Hg) are avoided. Difficulty in resolving this variability is further compounded by the fact that oxygen dissociation curves for fetal hemoglobin are significantly different from that of the adult hemoglobin and the ratio of fetal to adult hemoglobin is variable over the first 3 months of life and is usually unknown.

For neonatal monitoring a blood gas device that can estimate Pa_{O_2} within 10 to 20 mm Hg is required. Response time of the order of minutes is acceptable. Because hyperoxemia is better tolerated in adults and children than in neonates and infants, a monitor that measures Sa_{O_2} would suffice for monitoring adults and children. This is so because an acceptable Sa_{O_2} resides on the flat portion of the curve and would include a range of Pa_{O_2} higher than desirable for neonates.

Although CO_2 is physiologically con-

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trolled within a narrow range, changes of ±5 mm Hg are commonly encountered without adverse effects. Therefore, the ability to monitor changes in $Paco_2$ within that same range is clinically acceptable. Whereas $Paco_2$ can be altered by changes in ventilation within seconds, the strong influence of $P\bar{v}co_2$ on $Paco_2$ limits the physiologic response time to major changes of $Paco_2$ to 3 to 5 min. So ideally, $Paco_2$ monitoring should have an equivalent response time.

Monitoring During Anesthesia

Patient assessment during administration of anesthesia includes monitoring for physiologic stability and patient safety. The purpose of safety monitoring is to prevent iatrogenic harm to the patient caused by failure of the oxygen supply, accidental incorrect setting of fresh gas flows, inadvertent esophageal intubation, etc. A real-time, on-line monitor of patient oxygenation can offer major advantages in anesthesia safety monitoring. Early warning of oxygen desaturation affords the opportunity for a timely and appropriate response to prevent hypoxic injury. Trade-offs between response time and accuracy should therefore favor response time. Response times of the order of a few seconds are desirable.

Physiologic and safety monitoring of CO_2 is done to assure that ventilation is adequate to meet the demands of CO_2 production and elimination. The advantage of a real-time, on-line measurement over intermittent arterial sampling to monitor changing alveolar ventilation and CO_2 production is clear. Block (1) and Whitcher and associates (2) have proposed standards for assessing monitoring equipment needs during anesthesia that will add to those proposed by Harvard (3) and the American Society of Anesthesiologists (ASA) (4). CO_2 monitors that provide response times of a few seconds are perferred.

Exercise Testing

Performing arterial puncture to obtain Pao_2 and $Paco_2$ in an exercising patient may be difficult, intrusive, and inconvenient. It is also clear that the timing and frequency of arterial blood sampling is important, as blood sampled immediately *after* exercise does not reflect pulmonary gas exchange *during* exercise (5). Arterial blood sampling during exercise almost always requires an indwelling arterial catheter. Thus, reliable noninvasive means of continuous assessment of Pao_2 and $Paco_2$ would be of significant value during exercise testing.

Arterial hypoxemia during exercise is the finding most often evaluated. Noninvasive oximeters are useful in identifying patients with $Sao_2 < 95\%$ and $Pao_2 < 60$ mm Hg. They are less useful in the range in which large decreases in Pao_2 are reflected by only small changes in Sao_2, that is, above a Pao_2 of 60 mm Hg. This limitation of pulse oximeters may be important if noninvasive oximetry is used to select those patients who should have an arterial catheter during exercise.

The response time of a noninvasive oximeter is a second factor that must be considered as a subject with heart and lung disease has limited exercise tolerance. The response times of the monitors should be fast enough to follow potential changes in arterial gas tensions during rapidly progressive exercise protocols. An acceptable 90% response time for blood gas monitors should be within 20 s if clinically significant hypoxemia (or hypercapnia) at maximum exercise is not to be missed in patients who are unable to exercise for longer durations than 8 to 10 min during a progressive exercise test.

Finally, if noninvasive blood gas devices are used to monitor exercise testing on treadmills or on cycle ergometers movement can result in motion-induced artifacts that provide spurious oxygen saturation values. Insensitivity to movement should be a prime requirement of an acceptable device for use during exercise.

Sleep Studies

Whereas the directly measured arterial blood Pao_2 or Sao_2 and $Paco_2$ are inherently more accurate than noninvasive estimates, such static measurements do not characterize the rapidly changing oxygenation or carbon dioxide retention associated with respiratory disturbances during sleep (6).

Although normal subjects may show an increase in $Paco_2$ of 4 to 6 mm Hg in sleep, some patients may experience a > 20 mm Hg rise during sleep when significantly exacerbated during oxygen supplementation (7). Repetitive monitoring of alveolar ventilation by $Paco_2$ is not practical during routine monitoring of sleeping subjects because arterial punctures may cause arousal while arterial catheters can be uncomfortable or create potential hazards in restless sleeping subjects (8).

Technical requirements for noninvasive monitoring of sleeping subjects include the following: (*1*) minimal subject interaction requirements such as monitoring site changes, or other influences that disturb the subject's sleep or restrict body movement during sleep; (*2*) 90% instrument response time of ≤ 10 s for oximetry with a relative and/or absolute accuracies of ±2% saturation; (*3*) 90% instrument response times of < 1 min for carbon dioxide with a relative and/or absolute accuracies of ±5 mm Hg.

Apparatus Description and Clinical Performance

Transcutaneous Oxygen Measurement ($Ptco_2$)

Description and specification. This instrument is designed to measure the tension of oxygen at the skin surface using a modified Clark electrode (9) under the condition of minimal oxygen concentration gradient across the cutaneous diffusion barrier. Achievement of this condition places limitations on the electrical current requirements of the oxygen electrode. Skin conductance measurements performed by Eberhard and Severinghaus (10) indicate that with current sensor technology, the oxygen tension gradient across the skin is as low as 5%. Thus, oxygen tension at the surface of the skin is likely to be *correctly* measured. However, a serious problem encountered with this methodology stems from the dependence of the surface oxygen tension on the two physiologic factors—cutaneous blood flow and metabolism (11). Highly variable cutaneous blood flow is commonly encountered in acutely ill patients. Although cutaneous metabolism lies outside the control of instrumentation, localized application of heat can be used to increase perfusion and thereby reduce the influence of cutaneous blood flow on the $Ptco_2$ value. (Heat also increases the Po_2 of the capillary bed by decreasing the aqueous O_2 solubility providing an apparent offset to the drop in tissue Po_2 due to metabolism). A skin temperature of approximately 43° C is required to maintain adequate perfusion and dictates site changes at 4- to 6-h intervals to avoid thermal injury to the skin (12). Additional technical features of the $Ptco_2$ monitor that limit its usefulness include a recording delay during the warm-up period after site changes and slow response times that do not accurately reflect rapid changes in arterial Pao_2 (13–15). In fact, in adults, the strong influence of cutaneous blood flow has led to the use of transcutaneous O_2 monitoring as a measure of local perfusion (16, 17) rather than as an estimate of arterial Pao_2.

Transcutaneous oxygen monitoring is more effective for following Pa_{O_2} in neonates (18) who have a thin, immature epidermis. It is usually assumed that this increased effectiveness is primarily due to the reduction in the barrier to diffusion of oxygen; however, based on the Eberhard and Severinghaus adult gradient experiments referred to previously (10), this increased effectiveness must be primarily the result of diminishing metabolism associated with the thin epidermis.

The polarographic (Clark) electrode has also been adapted to fit in the palpebral conjunctival bed of the eye (19) and was for a short time commercially available from Orange Medical (Orange County). The response characteristics of the conjunctival electrode are similar to the Ptc_{O_2} monitor.

Clinical performance. **Critical care.** Ptc_{O_2} using a modified Clark electrode has received wide acceptance in neonatal and infant monitoring (13) and is of potential value in monitoring pediatric intensive care unit (ICU) patients (14, 20). In the adult, however, Ptc_{O_2} does not consistently correlate with Pa_{O_2}. The Ptc_{O_2} is generally 20 to 50% lower than the Pa_{O_2} due to a variety of factors that determine the efficiency of O_2 delivery to the heated skin (21–23). Ptc_{O_2} changes may reflect changes in Pa_{O_2}, cardiac output, or cardiovascular reflexes that change perfusion to the skin surface beneath the electrodes. What remains unclear from the literature is how often in the clinical setting does the Ptc_{O_2} change spuriously, leading to unnecessary additional patient evaluation with arterial and venous blood and cardiac output measurements? It is also unclear how often changes in Ptc_{O_2} can provide early signs of change in oxygenation or oxygen delivery that are clinically useful in reducing morbidity or mortality, improving patient management, or reducing the cost of blood gas and cardiac output determinations.

Ptc_{O_2} monitoring offers advantages for neonatal and young infant care due to the fortuitous physiologic advantage offered by the thin, underdeveloped infant skin, which has low metabolism for a given cutaneous blood flow. The noninvasive application also obviates the difficulty in obtaining frequent blood samples for Pa_{O_2} monitoring when access through the umbilical artery is not available. The direction and percentage change in Ptc_{O_2} generally correlates well with Pa_{O_2}, and under some circumstances Ptc_{O_2} can approximate Pa_{O_2}. However, it should also be understood that these correlations may be quite poor in older infants (24).

Under carefully controlled conditions in which the transcutaneous oxygen device is scrupulously maintained and calibrated *in vitro* and *in vivo*, Ptc_{O_2} will correlate well with oxygen tension and provide an estimate of the oxygen tension values that can guide therapy so that hyperoxemia ($Pa_{O_2} > 100$ mm Hg) and hypoxemia ($Pa_{O_2} < 50$ to 60 mm Hg) may be avoided (25). In situations in which arterial blood gas measurements are seldom done, the Ptc_{O_2} information may be no better than arterialized capillary oxygen tensions, which are limited in predicting hypoxic or hyperoxic conditions (26). Most clinicians would agree that Ptc_{O_2} monitoring is an adjunct to Pa_{O_2} assessment, but without blood gas correlations Ptc_{O_2} is of limited value. In combination with arterial gases and with a continuous recording, Ptc_{O_2} monitoring provides more dynamic information than static blood gas values alone even if these static measurements are performed frequently. In addition, a 24-h histogram plot may provide an estimate of the stability or instability of the infant and the response to therapeutic interventions.

Monitoring during anesthesia. In the controlled setting of surgery, usually < 4 h, the application of Ptc_{O_2} monitoring would seem feasible and appropriate. However, there are a number of disadvantages. The relatively slow response time for acute changes in FI_{O_2} or Pa_{O_2} may be too long for intraanesthetic situations (27). Cutaneous vasoconstriction or changes in cardiac output may occur during major surgery, resulting in a disparity between Pa_{O_2} and Ptc_{O_2}. Changes in cardiac output due to anesthetics or other drugs, the use of vasoconstrictive drugs, blood loss, and intraoperative heat loss may also lead to cutaneous vasoconstriction.

Transcutaneous monitoring has been used in anesthetized adults receiving a variety of agents (28–30). It has been demonstrated that both halothane and nitrous oxide can be reduced at the surface of a polarographic oxygen electrode, causing electrode current to drift upward and thus report falsely high oxygen tension values (31–34). Tremper and colleagues concluded that while this drift was statistically significant, it was clinically acceptable. For example, there was only an increase of 0.7 mm Hg/h of halothane exposure (35).

Ptc_{O_2} monitoring of neonatal or pediatric patients should be more effective than adult monitoring. From studies on neurosurgical patients, Glenski and Cucchiara suggested that transcutaneous oxygen monitoring was useful in detecting venous air embolism and detecting the attendant decrease in Pa_{O_2} (36). Conjunctival Po_2 has been suggested for monitoring cerebral blood flow during carotid surgery (37). However, there has been no critical review of the routine use of Ptc_{O_2} during anesthesia. Indeed, the introduction of pulse oximetry has largely replaced Ptc_{O_2} monitoring in the operating room.

Exercise testing. Ptc_{O_2} measurement during exercise as an estimate of Pa_{O_2} has been reported in only a few studies (38–41). Because a close relationship between Ptc_{O_2} and Pa_{O_2} is highly dependent on maintenance of adequate cutaneous blood flow, the $Pa_{O_2} - Ptc_{O_2}$ difference might be expected to show variability during exercise. In some studies, Ptc_{O_2} approximates Pa_{O_2} moderately well at rest and during exercise in normal subjects (38, 39), but differences (8 to 20 mm Hg) were found in other studies (38, 40). These exceed the technical limits suggested previously. A second problem is the slow response time of Ptc_{O_2} monitors during rapidly progressive exercise protocols. For example, Schonfeld and associates (39) reported the 90% response time for Ptc_{O_2} after a step change in inspired O_2 concentration to be 182.5 ± 7.9 s during exercise. Thus, it is possible that clinically significant arterial hypoxemia at maximum exercise could be missed using a Ptc_{O_2} monitor if the patient were unable to sustain high exercise intensity. This limitation may be less severe during steady-state exercise protocols, but is still likely to be important at high work rates or at the end of exercise. In light of the unpredictable correlation of Ptc_{O_2} with Pa_{O_2} and its slow response characteristics, monitoring of Ptc_{O_2} is not useful in assessing Pa_{O_2} during exercise.

Sleep studies. The usefulness of Ptc_{O_2} monitoring in sleep evaluation in the adult is limited by the need for 3 to 4 hourly site changes, the recording delay during the warm-up period after site changes, and by its slow response (41–43). Modification of the relationship between Ptc_{O_2} and Pa_{O_2} has been shown to be too variable to meet the technical requirements for sleep studies (44). These limiting features are not so troublesome in noninvasive oximetry.

Noninvasive Oximetry

Description and specifications. The technical objective of noninvasive oximetry is to measure the oxygen saturation of blood by observing absorption of optical waves as they pass through the skin and interact with red cells. The relation-

ship between cutaneous So_2 and Sao_2 is closer than the relationship between $Ptco_2$ and Pao_2 because the mean oxygen saturation of the tissue blood that is measured is much less influenced by metabolism than is the PO_2 of tissue with its low oxygen solubility. However, the oxygen saturation of tissue that is largely capillary blood is significantly influenced by the cutaneous metabolism/perfusion ratio.

Nonhematogenous factors as well as hematogenous factors influence the measurement of cutaneous So_2. An example of a nonhematogenous factor is skin pigmentation, which has an optical absorbency overlapping the absorbance curves of oxyhemoglobin (Hbo_2) and deoxyhemoglobin (Hb). Examples of hematogenous factors confounding the measurement are carboxyhemoglobin (Hbco) and methemoglobin (HbMET).

The first noninvasive oximeter was developed in Germany in 1932, but the use of a one wavelength light source restricted the device to research applications (45). A two wavelength ear oximeter was later reported by Wood and Geraci (46); however, the eight wavelength ear oximeter developed by Shaw (47) and marketed by Hewlett-Packard (HP; Waltham, MA) was the first oximeter to be widely applied in clinical applications. The eight wavelengths (using one for each significant nonhematogenous and hematogenous spectral interference) (48) would sum to give this instrument the capability to derive a cutaneous (So_2) measurement quite independent of a variety of spectral interferences. For example, a study by Ries and colleagues (49) reported no systematic differences between "darker pigmented subjects" and "light-pigmented subjects." Even though pigmentary influences can be minimized, cutaneous So_2 measurements remain highly dependent upon arterialization of capillary blood. The HP oximeter attempted to improve arterialization by heating the ear to 42° C.

The advantages of the HP ear oximeter included ease of equipment calibration, noninvasive patient application, and rapid response to changes in Sao_2 (21, 50–53). In the range of 60 to 100% saturation, the HP ear oximeter is accurate to within 2 to 4% of the value directly measured from arterial blood (6, 50, 52–55). However, instrument cost and inconvenience of the earpiece attachment limited the overall popularity of this instrument. The development of less expensive and more convenient pulse oximetry technology led ultimately to the discontinuation of development and manufacture of the HP oximeter.

Pulse oximetry replaced the measurement of the average transmitted light signal with a pulsatile light signal associated with volume changes in cutaneous blood in response to a stream of pressure pulses. As recognized by Nakajima and coworkers (56), changes in light absorption by tissue due to pulsatile changes in the blood volume of that tissue contain So_2 data that are specific to the respective blood phase (48). Use of this pulsatile data, formerly regarded as noise (57), eliminated the mathematical requirement for multiple specific light sources needed to handle spectral interferences from nonblood sources, specifically eliminating the spectral interference of skin absorbency. Of equal importance is the extent to which pulse oximetry (Spo_2) measurements reflect arterial as opposed to capillary So_2 values. Because the pulsatile signal is principally derived from the higher pressure vessels, the pulse oximeter measurement should be much less dependent on capillary "arterialization" than the HP oximeter.

Data obtained from methodology that uses a pulsatile instrumentation led to the development of oximeters that required only two light sources of different wavelengths to distinguish absorbance of blood components only. The concomitant development of ultrabright infrared light-emitting diodes (LED) having a wavelength of 930 μM and a high power red LED (660 μM) provided the necessary light sources currently used in pulse oximeters. Figure 1 shows the power spectrum of these LED in relationship to the absorbance spectrum of Hb and Hbo_2. Computational problems caused by scattering and the non-ideal nature of the LED spectral characteristics have been virtually eliminated by the use of powerful, but inexpensive and compact microprocessors. Accurate processing presupposes that the spectral characteristics of the particular LED are contained in the processor's data base. However, inherent variability in spectral characteristics of LED are the source of several technical problems that can limit the accuracy of the Spo_2 measurement. Variability in the LED spectral characteristics associated with manufacture is minimized by some manufacturers by LED selection and/or coding techniques. The influence of temperature on the LED spectral profile has led some manufacturers to place a temperature sensor in the vicinity of the LED to permit LED temperature spectral correction.

The scattering of transmitted LED light by variable tissue composition and geometry can create computational challenges. Scattering results from the suspension of hemoglobin containing red cells in the blood and causes the mathematical description of absorption to deviate from the simple formulation of Beer's law. *In vitro* analytic instruments obviate this problem by lysing the red cells, creating the homogeneity required for Beer's law to be applied. The pulse oximeter solution is to create an empirical calibration curve for the instrument. This approach requires the red cell geometry of the patient being monitored to be identical to that of the subjects whose data were used to generate the instrument's calibration. This is not always the case, and empirical calibration data may contribute significantly to measurement error in patients having abnormal hemoglobin concentrations or hemoglobin disorders that produce unusual scattering patterns, such as sickle cell anemia and thalassemia.

The use of only two LED light sources limits the ability of Spo_2 data to be compensated for blood spectral interferences posed by Hbco, HbMET, and bilirubin. Fortuitously, neither Hbco or HbMET contribute significantly to the relationship between Spo_2 and *functional* Sao_2 (58, 59) (the fraction of chemically active Hb that is combined with oxygen), and the absorption of bilirubin is far enough into the blue portion of the light

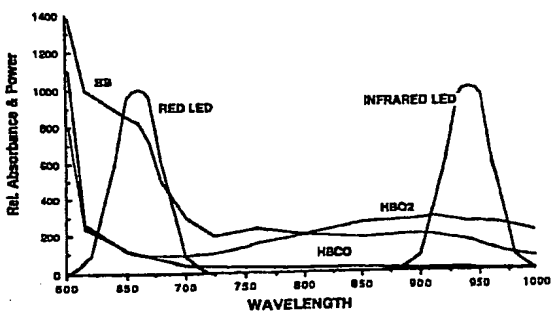

Fig. 1. The power spectrum of the ultrabright infrared LED (930 nM) and the high-power red LED (660 nM) in relationship to the absorbance spectrum of Hb, Hbo_2, and Hbco.

spectrum that little interference would be expected. However, no Spo_2 assessment of jaundiced patients has been reported.

The fact that adult and fetal Hbco have differences in their spectral absorption characteristics that lead to errors in measurement of fetal *fractional* Sao_2 (60) (the fraction of total hemoglobin that is combined with oxygen as measured by the IL282 CO-Oximeter; Instrumentation Laboratory), does not imply that measurements by an adult calibrated pulse oximeter should be significantly influenced by the presence of fetal hemoglobin. Because Hbco has no significant effect on the Spo_2 measurement and because the adult and fetal differences in Hbo_2 and Hb spectral absorptions are close enough not to require further Sao_2 CO-Oximeter correction beyond that needed to account for spurious Hbco measurements (60), spectral differences between adult and fetal hemoglobin should not result in Spo_2 measurement effects due to the presence of fetal hemoglobin. Assuming similar scattering patterns (similar red cell geometries), the performance of pulse oximeters should not be influenced significantly by the presence of fetal hemoglobin—a point advertised by Nellcor (Nellcor Pulse Oximetry Note #4, Hayward, CA).

One of the most common problems encountered with pulse oximetry is separating the changes in light absorption originating from arterial pulsation from artifact or noise. Noises created by movement and electrical interference may be inseparable from the decreased signal amplitude associated with vasoconstriction induced by low cardiac output or vasoactive drugs. Random noise, which produces equal signals at both measured wavelengths causes the Spo_2 value to become 85% (Justin Clark, unpublished observations). Attempts to minimize extremity movement has led to efforts to use alternative sampling sites such as the ear or conjunctiva, the nose, and forehead. The use of alternative sites may, however, be associated with reduced pulse signal compared with the finger site. The ear pulse signal reportedly has the advantage of improved signal strength during vasoconstriction or hypotension (61).

Advances in LED technology have led to simplification of the pulse oximeter ear probe and finger probe. The finger oximeters have become popular mainly because of the convenience and patient comfort associated with the finger site. However, one disadvantage of this site is that it requires 12 more seconds to detect changes in Sao_2 occurring at the finger when compared with the ear (62). Longer response times may also be expected when the toe is used as a monitoring site as is often the case of the pediatric patient. Data averaging schemes intended to improve accuracy and provide artifact rejection of pulse data further decrease the frequency response of these devices. Some manufacturers provide overrides for such software-imposed limitation on frequency response. Additional clinical studies aimed at comparing ear versus finger oximeter sites would be useful.

Clinical performance: critical care. **Neonates.** Because most workers prefer to base oxygen management on Pao_2 rather than saturation, pulse oximeters may be less applicable to neonatal monitoring because larger uncertainties exist in characterizing oxygen dissociation curves in neonates. Invasive Pao_2 measurements are required to correlate Spo_2 measurements with Pao_2; thus, oximetry without arterial blood gas determinations may be insufficient for neonatal care. However, oximetry can make it possible to be more selective about when arterial blood gas determinations are needed (63). Clinical studies in neonates suggest that oximetry can be useful for detecting hyperoxemia in spite of the relatively flat nature of the oxygen dissociation curve above 90% (64, 65). Finally, the shorter response time and ease of operation and application are attractive advantages of oximetry over $Ptco_2$ monitoring of neonates.

Children and adults. Because hyperoxemia is better tolerated in adults and older children than in neonates and infants, and because the relationship between Sao_2 and Pao_2 is also more predictable in the former groups, one would expect Spo_2 to be more useful for monitoring adults and older children than for monitoring neonates and infants in the ICU setting. The advantages of Spo_2 over $Ptco_2$ monitoring in adults, as summarized in table 1, suggest that pulse oximetry has value as a monitor in the adult ICU, although there have been no clinical studies to date confirming the value of pulse oximetry in the adult critical care setting. Given the limited ability of oximetry to predict the absolute value or trends of Pao_2 in patients with arterial and/or variable cutaneous perfusion, determinations of Pao_2 by arterial blood gas analysis are still necessary to assess accurately a patient's clinical course.

Clinical performance: long-term oxygen therapy. The report by Carlin and coworkers (66) comparing oximetry to arterial blood gas assessment demonstrated that as many as 40% of individuals were erroneously identified by ear oximetry as failing to meet the original Medicare guidelines for initiation of oxygen therapy. The Health Care Financing Administration (HCFA) in its Medicare guidelines required a Pao_2 of $\leq$ 55 mm Hg or Sao_2 of $\leq$ 85% as justification for initiation of oxygen therapy (67). Many of the Carlin study patients who were identified by oximetry as having > 85% arterial saturation levels had simultaneously measured Pao_2 levels < 55 mm Hg. A total of 80% of the patients with a resting Pao_2 of $\leq$ 55 mm Hg had an oximeter value of > 85%. These investigators cautioned that if oximetry alone is used to determine eligibility for Medicare guidelines, many patients may be denied the benefits of oxygen therapy. A conference report concluded that an oximetrically determined Sao_2 of 88% more closely approximates a Pao_2 of 55 mm Hg (68). The report further suggested that arterial blood gas assessment be used to document the medical necessity of long-term oxygen therapy.

Anesthesia. The easy application and fast response time of the pulse oximeter has led anesthetists to prefer this instrument to the transcutaneous oxygen monitor in the assessment of oxygen transport in patients during and after anesthesia and surgery. Spo_2 is now the most commonly used measurement in the care

TABLE 1

COMPARISON OF TRANSCUTANEOUS AND PULSE OXIMETRY

	Transcutaneous	Pulse
Accuracy in adult	No	Yes
Detection of high Pao_2	Yes	No
Set-up time	Minutes	Seconds
Time response	Minutes	Seconds
Measures pulse	No	Yes
Heated skin burns	Yes	No
Stability at one site	2–4 h	Yes
Motion artifact	Minimal	Yes
Sensitivity to perfusion	Great	Some, but detected as problem

of patients undergoing anesthesia (69). The recently published standards of practice for intraoperative monitoring (3) suggest that pulse oximetry as a monitor of the status of the circulation and oxygenation is acceptable. The ASA, in October 1989, amended its monitoring standards to mandate pulse oximetry during anesthesia of all types (4).

Some limitations of pulse oximetry during surgery should be recognized. The use of methylene blue dyes during surgical procedures may result in transient but strikingly spurious low values (70–72). The effect of ambient and fluorescent light can also lead to false desaturation values and has led to innovative solutions such as covering the sensor with an aluminum foil packet to exclude extraneous light (73). Use of radio frequency current electrocautery in the operating room can occasionally interfere with the signal from the sensor of the pulse oximeter. Motion artifact can be a problem, but this is only seen in awake patients receiving local or regional anesthesia. When vasoconstriction during surgery results in signal loss from the extremity probe, substitution of an ear or bridge of the nose sensor may provide acceptable sensor output (74). Disparity between the electrocardiogram (EKG) heart rate and pulse oximeter pulse rate *may* also provide a clue to the source of inaccurate Sa_{O_2} assessment.

In summary, pulse oximetry is now widely used and indeed can be considered a mainstay of monitoring during anesthesia. Clinical studies designed to document better the accuracy and limitations of this technology in the operating room are needed.

Exercise testing. Noninvasive oximeters have been used during exercise to estimate arterial blood oxygenation in normal subjects and patients with a variety of disorders. Nonetheless, there are some important factors that should be considered when using this technology. Ries and associates (49) stressed that particular care in stabilizing the ear oximeter sensor was required to obtain satisfactory results because of movement of the exercising patient. In 14 patients referred for clinical exercise testing, Hansen and Casaburi (75) studied relationships between measured arterial blood saturation and pulse oximeter values. In seven patients there was good agreement at all times during rest and recovery, and in two patients the pulse oximeter overestimated arterial blood So_2. However, in five patients the pulse oximeter underestimated the arterial So_2 (mean 84 versus 96%) during exercise, although values became closer during the recovery phase. The investigators surmised that this variability may result from local blood flow limitation.

In another comparison (76), the mean differences in resting and peak exercise O_2 saturation measurements by pulse oximetry and direct arterial blood sampling were as large as 5.0% at rest and 13.6% during exercise. Williams and colleagues (62) found substantial decreases in O_2 saturation by pulse oximetry in 10 highly trained endurance runners during very intense exercise. Although these investigators concluded that the decline in O_2 saturation resulted from diffusion limitation across the lungs, Hansen and Casaburi (75) have suggested that it may have been due to reduced earlobe perfusion during exercise.

There have been many reports of satisfactory use during exercise of a nonpulse oximeter (49, 77, 78), but because of differences in methodology it cannot be assumed that pulse oximeters are similarly useful. Most studies of the general clinical accuracy of pulse oximetry have not been performed during exercise. Further studies of the role of blood flow, movement artifact, and specific methodology are needed to validate pulse oximetry during exercise studies. If there is any clinical suspicion of arterial oxygen desaturation during exercise that is not elucidated using the pulse oximeter, then arterial blood gases should be obtained.

Sleep studies. The introduction of the HP ear oximeter in the 1970s heralded a new era for continuous monitoring of oxygen saturation during sleep (6), primarily because of the clinical advantages of noninvasive patient application and a rapid response to changes in oxygen saturation (21, 50–53). The pulse oximeter, by not requiring the heating of tissues and providing a simplified ear probe, has removed problems associated with thermal stimulation and skin traction during body movement in sleep so that accurate assessment of posturally induced breathing disturbances is now possible. Also, the use of a double-adhesive pad minimizes detachment of the ear probe and minimizes motion artifact during sleep monitoring (79).

In sleep studies, pulse oximeters measure Sa_{O_2} with an accuracy of 2 to 6% when compared with arterial blood-derived determinations of any Hb in the range of saturations of 75 to 100% (55, 80–82). However, the ear oximeter may underestimate arterial blood oxygen saturation or provide no signal when reduced perfusion is associated with vasoconstriction or hypotension; nonetheless, at least one study demonstrated satisfactory correlation during vasopressor therapy and vasodilator-induced hypotension (82). Even though such pathophysiologic events are rarely encountered in assessment of ambulatory patients in sleep laboratories, such perfusion abnormalities may impair the accuracy of ear oximetry when assessing breathing disorders during sleep in the unstable critically ill patient.

Transcutaneous CO_2 Monitoring (Ptc_{CO_2})

Description and specifications. In 1793, John Abernathy, an English surgeon, demonstrated that CO_2 was released from human skin. Nearly 200 yr passed before technology led to the successful application of the Stowe-Severinghaus electrode (83) and later still to an infrared sensor (84–87), which could be applied to monitor transcutaneous CO_2. The Stowe-Severinghaus electrode has been well described (88). It consists of a small pH electrode surrounded by a heated collar within which is a silver sleeve in normal saline. The collar heats the skin and the silver-silver chloride acts as a reference electrode. A gas-permeable membrane is mounted above the skin surface with an interposed solution of chloride and bicarbonate ions in an ethylene glycol hydroxycellulose base.

By contrast, the HP Ptc_{CO_2} device uses the infrared transcutaneous capnometer. With this device, CO_2 from the skin enters a gas-phase sample chamber where CO_2 is analyzed using an infrared sensor. Although the gas volume of the sample chamber (50 μl) is small for infrared absorption technology, it is large relative to the volume of the bicarbonate buffer solution that covers the pH sensors of the Stowe-Severinghaus device. This larger gas volume sample requirement leads to a very slow response time. If the area of the gas collection manifold is increased, this difficulty can be partly overcome. However, the lower limit of the CO_2 gas volume per unit of diffusion area is still larger than that of the Stowe-Severinghaus probes. The response time can be further reduced by mild skin abrasion, which reduces the diffusion barrier by removing the stratum corneum.

Just as with the transcutaneous O_2 measurement, transcutaneous CO_2 devices measure the CO_2 tension at the surface of the epidermis (Ptc_{CO_2}), not the $Paco_2$. However, the high CO_2 tissue solubility reduces the apparent depen-

dency of the $Ptcco_2$ on tissue metabolism relative to the $Ptco_2$ by a factor that is likely of the order of 20. It is this reduced $Ptcco_2$ influence on the cutaneous perfusion/metabolism ratio that provides opportunities for $Ptcco_2$ monitoring in many clinical situations in which $Ptco_2$ monitoring has not been found to be useful. This reduced metabolism also reduces the technical need for heat-induced vasodilation, which in turn reduces the need for frequent site changes to prevent heater-induced burns and skin ulcers. Eletr and associates (89) reported good correlations between $Paco_2$ values and capnometer $Ptcco_2$ values measured at 39.5° C, a temperature at which site changes in hemodynamically stable patients are not required. However, they credited the stripping of the stratum corneum with its attendant mild trauma with causing cutaneous vasodilation equivalent to the vasodilation produced by 43° C skin temperatures. Such stripping procedures and/or low temperature operation have not been reported for Stowe-Severinghaus sensors. The lowest reported operating temperature for satisfactory response time of the Stowe-Severinghaus device is 42° C (90).

Tremper and colleagues (91–93) and Nolan and Shoemaker (94) studied 44 patients in either the ICU or operating room and found that $Ptcco_2$ was 23 ± 11 mm Hg above $Paco_2$, with an r of 0.8 in 411 data sets in patients with a cardiac index (CI) > 1.5 l/min/mW. When the CI was < 1.5, the (Ptc − Pa)CO_2 gradient increased dramatically, suggesting that electrode heating or vasoactive medications may not enhance skin perfusion in shock or low perfusion states (91).

The solubility characteristic of CO_2 that is responsible for the diminished effect on $Ptcco_2$ of the cutaneous perfusion/metabolism ratio has an intrinsically adverse effect on the response time of the $Ptcco_2$ measurement sufficient to limit the usefulness of $Ptcco_2$ monitoring for some applications. Response time is multifactorial, comprising both physiologic and instrumentation elements. In addition to CO_2 tissue solubility, the physiologic time constant is influenced by the ratio of tissue to capillary volume, capillary blood flow, and tissue diffusivity.

The instrument time constant is proportional to the CO_2 volume of the sensor (which for the Stowe-Severinghaus sensor is the product of the CO_2 chemical solubility and thickness of the bicarbonate buffer) and inversely proportional to the CO_2 diffusivity of the membrane and the uncatalyzed CO_2 hydration rate (85). Note that the chemical solubility of the bicarbonate buffer solution is strongly influenced by the concentration of the buffer.

The (*in vivo*) system time constant is approximated by the sum of the physiologic and instrument time constants. The instrument time constants have been reported between 7 and 26 s (85, 95) for Stowe-Severinghaus instruments. *In vivo* time constants have been reported in the range of 40 to 65 s (85) for an electrode with an instrument time constant of 26 s (glass pH sensor and standard 25-μm teflon membranes), giving a range for the physiologic time constant of 14 to 39 s. Nickerson and coworkers (95) measured average physiologic CO_2 response times of 60 s and 23 s under conditions of rest and exercise, respectively. McLellan and colleagues (96) reported total HP capnometer time constant measurements of 2.25 to 3 min (*in vivo*). Assuming a physiologic time constant range of 14 to 60 s, the McLellan data provide a capnometer instrument time constant estimate of 2.0 min.

Because CO_2 solubility in tissue and plasma is temperature dependent, the $Ptcco_2$ measurement is similarly affected by skin temperature. This temperature dependency increases Pco_2 4.5% for every degree centigrade rise in temperatures. The temperature sensitivity of the pH glass electrode causes $Ptcco_2$ to rise an additional 4% for every degree centigrade rise. The net effect of heating the skin is that $Ptcco_2$ overestimates arterial Pco_2 by a factor of 1.31 to 1.61 (86, 87). As a result, $Ptcco_2$ will be unacceptably high compared with $Paco_2$ unless the instrument is calibrated and adjusted to account for such influences. Newer models of $Ptcco_2$ monitors incorporate a temperature correction factor based on regression analysis of a data set from a large population (97).

Clinical performance. **Critical care.** $Ptcco_2$ has been demonstrated to be clinically useful in monitoring adult patients in the ICU setting. A pH sensor made of iridium/iridium oxide material was reported by Williams and associates (90) to be useful in 27 adult surgical patients with high fever. In 127 data sets, r was 0.84 with a standard deviation (SD) of ±5.2 mm Hg and a mean (Ptc − Pa)CO_2 gradient of 20 mm Hg. Mahutte and colleagues (97) reported 514 simultaneous $Ptcco_2$ and $Paco_2$ measurements in 47 adult ICU patients and found excellent coefficients (r = 0.93 to 0.95) when measurements were made within 4 h of calibration. However, Mahutte's group also reported that 16% of the $Paco_2$ changes were in the opposite direction to changes in $Ptcco_2$. When the $Paco_2$ change was > 5 mm Hg, the direction of change was the same with both techniques.

There have been many reports indicating that $Ptcco_2$ monitoring using the infrared device provides clinically useful data in hemodynamically stable adult subjects (89, 96, 98). Eletr and associates in 1978 (89) studied 25 patients during weaning from the ventilator in an ICU. In the $Paco_2$ range from 25 to 70 mm Hg, they showed an excellent correlation between the two techniques (mean [Ptc − Pa]CO_2 of 5.2 mm Hg with an SD of 1.5 mm Hg). Although the (Ptc − Pa) CO_2 gradient was not predictable from patient to patient, it did remain constant in any given patient during the weaning period. Greenspan and colleagues (98) made 60 measurements in 13 hemodynamically stable patients and the mean (Ptc − Pa)CO_2 was 4 mm Hg. McLellan and coworkers (95) studied nine healthy subjects and six patients and they too found excellent correlation (r = 0.98) and a small (Ptc − Pa)CO_2 of 4 mm Hg.

Many clinical studies in neonates have shown good correlations between $Paco_2$ and $Ptcco_2$. In 1985, Rithalia (99) reviewed nine studies that included 210 neonates and found correlation and coefficients of cutaneous CO_2 to arterial CO_2 ranging from 0.85 to 0.98, with most being > 0.94. $Ptcco_2$ monitoring provides an ideal method to observe trends in $Paco_2$ with changes in therapy or changes in the infants' state when asleep, awake, and with agitation. As with $Ptcco_2$ monitoring, the ideal $Ptcco_2$ application is when arterial blood gas measurements are available so that both *in vitro* and *in vivo* correlations are possible.

The wider application of $Ptcco_2$ monitors has been limited by the high cost of the devices and the slow acceptance by clinicians. Combined transcutaneous O_2/CO_2 probes are finding increased acceptance for monitoring patients when both O_2 and CO_2 monitoring is desirable. However, because the combination probe must be heated to above 43° C, relocation of the probe to a new site is necessary every 3 to 4 h depending on the susceptibility to thermal injury in the individual patient.

Anesthesia. The validity of $Ptcco_2$ monitoring has been generally accepted in anesthesia patients (28–30, 36, 100, 101). Rafferty and coworkers (30) studied 30 adult neurosurgery patients and

found no effect of nitrous oxide, enflurane, or fentanyl anesthesia on the Ptc_{CO_2} measurements. Disadvantages of transcutaneous measurements include long response times and the need for site changes.

Exercise testing. Ptc_{CO_2} monitoring devices fail to meet the response time requirements for noninvasive exercise testing of blood gases leaving $P_{ET}CO_2$ monitoring as the remaining noninvasive alternative for monitoring Pa_{CO_2}.

Sleep studies. Noninvasive Ptc_{CO_2} monitoring may be especially applicable for patients with waking hypercapnia or symptoms of morning headache (7, 102). Ptc_{CO_2} monitoring is useful for monitoring alveolar hypoventilation during sleep. Ptc_{CO_2} monitoring has been used to assess the efficacy of nasal/oral ventilation during sleep. While infrared or Stowe-Severinghaus Ptc_{CO_2} electrodes are useful in detecting trends in alveolar ventilation, their slow response times prevent them from accurately depicting Pa_{CO_2} changes associated with brief apnea or hypopneas (8, 102). Wider application of Ptc_{CO_2} electrode monitoring has also been limited by the need for careful skin preparation, concurrent arterial blood gas measurement for calibration purposes, and the high cost of the monitoring device. Although the necessity for skin site changes is not as severe a drawback as with Ptc_{O_2}, because of its operation at a lower temperature (7, 8, 89, 96, 98, 102), the trade-off is prolonged response time. This is particularly true for the infrared devices.

Airway Carbon Dioxide Monitoring

Description and Specifications. Airway CO_2 can be monitored continuously by either infrared spectrophotometers or respiratory mass spectrometers. The former lend themselves to freestanding units, whereas the respiratory mass spectrometers (103) and monitors using thermal and Raman scattering principles are more commonly used during anesthesia gas monitoring because of their multiple gas analysis capabilities.

Freestanding units are of two types: inline and sidestream monitors. The inline CO_2 sensor is connected directly to the endotracheal tube and receives the total alveolar gas flow; whereas, the sidestream type receives a portion of the alveolar flow via a side port connector. The inline type has the intrinsic advantage of maximal frequency response and minimal delay and is therefore most suitable for infants. Disadvantages of the inline type include calibration inaccuracy while in use and the encumbrance of a sensing unit at the patient interface. These technical factors have been minimized in new in-line end-tidal monitors, such as the HP. However, even though the sensor and connectors have low dead space and low resistance and the transducer is sufficiently light to prevent tethering or kinking of the endotracheal airway or tracheotomy tube, the weight of the transducer and its associated connections may still restrict patient movement and may necessitate sedation of restless patients. The sidestream monitor adds essentially no encumbrance to the patient interface and has the additional advantage of in-use calibration capability. However, in order to achieve adequate frequency response, sidestream flows between 125 and 500 ml/min are required. These rates are too high for accurate end-tidal measurements in neonates and infants.

The peak expired CO_2, which is usually the $P_{ET}CO_2$, will approximate Pa_{CO_2}, assuming the following conditions: (*1*) CO_2 equilibrium is achieved between end-capillary blood and alveolar gas, (*2*) $P_{ET}CO_2$ approximates the time-weighted average of the ventilation-weighted Pa_{CO_2}, and (*3*) the lung is sufficiently uniform in terms of ventilation to perfusion ratio ($\dot{V}/\dot{Q}$). Strong experimental support for the first condition was first reported by Scheid and associates (104) and later by Clark and colleagues (105) in response to a mounting body of evidence to the contrary that had led to the controversial CO_2 active transport mechanism proposed by Gurtner and coworkers (106, 107). Plausible explanations for results from the most challenging of these reports of positive gas-to-blood Pc_{O_2} gradients that triggered the controversy have been provided by Scheid and Piiper (108, 109).

Condition 2 (see previous paragraph) cannot be met exactly for $P_{ET}CO_2$ because the end-tidal point is close to the maximum alveolar CO_2 value in the respiratory cycle. Theoretically, the end-tidal value should be about 2% higher than the time-weighted mean in normal resting subjects (110) and about 4% higher in exercising subjects (111), assuming tidal volumes are large enough to displace dead space. Positive (Aa) CO_2 gradients from this source can be further increased by factors that increase the cyclic variation of Pa_{CO_2} differences, such as low cardiac output and decreased respiratory rate. Such gradients can also be influenced (increased or decreased) by the pattern of ventilatory flow (111).

Condition 3 can be approached in normal subjects. (Normal $\dot{V}/\dot{Q}$ nonuniformity produces a decrease in $P_{ET}CO_2$ of about 2%, which tends to compensate for the increase related to Condition 2 above.) Because $P_{ET}CO_2$ is ventilation-weighted whereas Pa_{CO_2} is perfusion weighted, $P_{ET}CO_2$ moves in the direction of the inspired CO_2 tension whereas Pa_{CO_2} moves in the direction of the mixed venous CO_2 tension—a condition that must cause the $AaCO_2$ gradient to become negative as $\dot{V}/\dot{Q}$ nonuniformity increases. However, it should be noted that in the presence of significant asynchronous ventilation, $\dot{V}/\dot{Q}$ nonuniformity does not necessarily force the Aa gradient CO_2 to be negative. The trend toward negative $P_{ET}CO_2$-Pa_{CO_2} gradients is reduced or even reversed if the phasing of expiration is such that the low $\dot{V}/\dot{Q}$ compartments empty toward the end of the respiratory cycle. The effectiveness of using $P_{ET}CO_2$ as an indicator of Pa_{CO_2} is heavily dependent on the degree and variability of the patient's $\dot{V}/\dot{Q}$ distribution. In patients with extreme $\dot{V}/\dot{Q}$ nonuniformity such as pulmonary emboli, the adult respiratory distress syndrome, and chronic obstructive pulmonary disease (COPD), negative Aa CO_2 gradients exceeding 20 mm Hg may be observed (112). However, despite the recognized difficulties and variations in the gradients, airway CO_2 monitors are now frequently used both as freestanding units as well as units integrated into newer mechanical ventilators and anesthesia gas monitoring systems.

Although $P_{ET}CO_2$ recordings can be used with a face mask and nasal cannula, there is always the potential for gas dilution by ambient air, and hence the accuracy of the measurement of alveolar carbon dioxide tension may be compromised. Accurate $P_{ET}CO_2$ cannot be achieved during nasal continuous positive airway pressure ventilation because of continuous flow through the mask leak.

The best measure of $P_{ET}CO_2$ will be obtained when (*1*) tidal volumes are large enough to displace dead space; (*2*) fresh gas flow rates are low enough to prevent dilution or washing out of CO_2; (*3*) sample aspiration rates are low enough that they do not interfere with patient ventilation or entrain air that may dilute the CO_2; (*4*) the sampling site is close to the patient, minimizing the dead space; and (*5*) the waveform is displayed for end-tidal alveolar plateau analysis (113). Despite the use of elegant mucus traps and filters, occlusion of sampling lines and sensor by aspirated mucus and debris is a common clinical problem.

Clinical performance. **Critical care.** It is apparent from the previous section that the $P_{ET}CO_2$ will be most difficult to measure in neonates or young infants who have small tidal volumes, with relatively high ventilatory rates and airway resistances. The difficulty is made worse when neonates or infants are mechanically assisted by ventilators that require large fresh gas flow rates and the $P_{ET}CO_2$ is measured by an instrument with a high sample aspiration rate relative to the patient's own minute volume of ventilation. Epstein and colleagues (114) evaluated the use of $P_{ET}CO_2$ with $PtcCO_2$ in critically ill newborn infants on ventilators. They determined that although $PtcCO_2$ measurements led to estimates of $PaCO_2$ with 95% confidence limits of ±6 mm Hg if properly calibrated, $P_{ET}CO_2$ was less reliable. They also noted that the sampling airway adapter led to CO_2 retention in more than half of the patients. Even in adult patients many factors produce artifacts that prevent accuracy and precision in estimating $PaCO_2$. Fallat and coworkers (115) reported that $P_{ET}CO_2$ would track $PaCO_2$ in 30 patients after cardiac surgery (mean $[P_A - P_{ET}]CO_2 = 4.8$ mm Hg). The gradients did not significantly change during weaning and extubation. In five COPD patients, the mean $(P_A - P_{ET})CO_2$ was higher at 9.4 mm Hg, but again would be used to monitor weaning. Hatle and Rokseth (112) have similarly reported on the use of $P_{ET}CO_2$ in a variety of patients with pulmonary emboli, COPD, and left ventricular failure. Though gradients were elevated, particularly in patients with massive pulmonary emboli and severe COPD, they noted that the gradients could be reduced with maximal expiration, which raised the $P_{ET}CO_2$ closer to the $PaCO_2$ in most patients but not in those with pulmonary emboli, and suggested this as a diagnostic benefit. It is of interest that in COPD patients, the $P_{ET}CO_2$ would increase to a level greater than the $PaCO_2$ on the maximum expiratory maneuver (112). Riker and Haberman (116) and McAslan (117) showed that by monitoring $P_{ET}CO_2$ they were able to reduce the need for arterial blood gas measurements, shorten weaning time, expedite detection of alveolar hypoventilation, and improve the management of patients with head injuries. Niehoff and associates (118) also demonstrated the usefulness of $P_{ET}CO_2$ monitoring in reducing arterial blood gas measurements during ventilator weaning.

In contrast to these findings, Yamanaka and Sue (119) found that although the difference between $P_{ET}CO_2$ and $PaCO_2$ correlated with the ratio of dead space/tidal volume in mechanically ventilated adult patients, the $PaCO_2$ could not reliably be estimated from $P_{ET}CO_2$ in the face of changing ventilation-perfusion relationships. Other investigators (116, 117) have shown that capnometry is fairly sensitive as an identifier of hypocarbia (33 of 39 episodes) and observed that capnometry is quite insensitive as an identifier of hypercarbia (25 of 91 episodes). Hoffman and coworkers (120) found good correlation of $P_{ET}CO_2$ and $PaCO_2$ in 20 critically ill patients; however, when ventilation was acutely altered to test the monitoring precision of $P_{ET}CO_2$, 4 of the 20 patients showed a negative correlation of $PaCO_2$ with $P_{ET}CO_2$, and the investigators warned that $P_{ET}CO_2$ monitoring may provide misleading trends of $PaCO_2$ when gradients of $P_{ET}CO_2 - PaCO_2$ change. Snyder and colleagues (121) reported 157 measurements of $P_{ET}CO_2$ and found 40 (26%) with $(Pa - P_{ET})CO_2 > +5$ mm Hg and 17 (11%) with over −5 mm Hg difference.

It is clear from these studies that there can be considerable variation in $P_{ET}CO_2 - PaCO_2$ gradients, particularly in response to changes in the distribution of ventilation and perfusion. The practice of using $P_{ET}CO_2$ as a relative indicator of $PaCO_2$ may be suspect when weaning from ventilatory support if ventilatory changes produce significant variation in the $\dot{V}/\dot{Q}$ distribution.

Anesthesia. The relative ease of $P_{ET}CO_2$ monitoring, and its usefulness as a physiologic and particularly as a safety monitor, has led to its acceptance and widespread use by anesthesiologists (122). Standards for monitoring during anesthesia, proposed by Block (1), Whitcher and associates (2), Harvard (3), and the ASA (4) all support the use of capnography for a variety of situations, but there are some caveats. In infants and small children (weighing 12 kg or less) ventilated with a partial rebreathing circuit, the sampling site becomes a significant dependent variable. Capnographic waveforms from distal endotracheal tube sampling sites must and do show constant plateau phases during expiration, whereas those from the proximal endotracheal tube sites fail to achieve a plateau and underestimate the $PaCO_2$ (123). This is consistent with the hypothesis that gas sampled at the proximal site is a mixture of expired alveolar gas and fresh gas removed from the circuit by sampling. During low-flow, closed-circuit anesthesia sampling rates should not exceed 250 ml/min in order to prevent interference with the patient's fresh gas flow (124).

In older children and adults using anesthetic circuits with unidirectional valves, capnographic studies during anesthesia have demonstrated the close relationship between $P_{ET}CO_2$ and $PaCO_2$ (125–128). Two studies (129, 130) report that $P_{ET}CO_2$ was useful for the early detection of endotracheal tube accidents, i.e., esophageal intubation, disconnection, and tube obstruction. However, Raemer and colleagues (131) reported that $PaCO_2$ assumptions based on $P_{ET}CO_2$ were not invariably reliable because the $(Pa - P_{ET})CO_2$ gradient was too variable.

Although the $P_{ET}CO_2$ is most useful when the $(Pa - P_{ET})CO_2$ gradient remains constant, a variable gradient must be expected. In situations in which $P_{ET}CO_2$ does not correlate with what the clinician expects, $PaCO_2$ should be measured as a guide for $P_{ET}CO_2$ tracking and interpretation (132). A change in the $(Pa - P_{ET})CO_2$ gradient in itself may indicate an important pathophysiologic change such as atelectasis, thromboembolism, or air embolism. The fall in $P_{ET}CO_2$ during venous air embolism (VAE) in neurosurgical patients correlates with the entrainment of air as it travels through the heart to the pulmonary microcirculation, leading to decreased lung perfusion and increased physiologic dead space (4). Capnography has also been useful in detecting the marked increases in CO_2 production during malignant hyperthermia in both swine and humans (133–135).

In sedated but spontaneously breathing patients undergoing regional or local anesthesia, $P_{ET}CO_2$ monitoring by nasal cannula may be less valuable because of entrainment of air into the sample. However, modifications to the sampling line have resulted in successful detection of ventilatory changes (136).

Exercise testing. $PtcCO_2$ monitoring devices fail to meet the response time specifications for exercise testing, leaving $P_{ET}CO_2$ monitoring as the remaining noninvasive alternative for monitoring $PaCO_2$. However, the variability of the $P_{ET} - PaCO_2$ gradient may limit the usefulness of $P_{ET}CO_2$ in exercise testing (137). Exercise by itself can increase the $P_{ET}CO_2 - PaCO_2$ gradient (138). $P_{ET}CO_2$ is not necessarily identical to $PaCO_2$ (137–139) even in normals. Jones and associates (139) reported the difference between $P_{ET}CO_2$ and $PaCO_2$ in five healthy young men during constant work rate exercise

on a cycle ergometer at 25 and 50% of maximum oxygen uptake. Differences between −2.5 and 9.1 mm Hg were observed and were dependent on respiratory frequency, tidal volume, and CO_2 output. The investigators presented a regression equation for estimating $Paco_2$ from $PETco_2$ that incorporated these variables. However, they warned that this formula was not to be used in patients with abnormal pulmonary function because the contribution of longtime constant ventilation regions would increase the difference between the two Pco_2 values. Hansen and colleagues (138) found that at the end of symptom-limited incremental cycle exercise, the (Pa − PET)CO_2 difference averaged −4.1 ± 3.2 mm Hg (range +1 to −14 mm Hg) in 77 middle-aged sedentary men without clinical evidence of lung or heart disease. In patients with pulmonary disease, the (Pa − PET)CO_2 difference can be large both at rest and during exercise (140, 141); this difference may be a useful marker of the presence of high ventilation-perfusion lung units analogous to the measurement of dead space/tidal volume ratio.

Monitoring $PETco_2$ is helpful to identify the anaerobic threshold during exercise (142) or to suggest hyperventilation. Thus, $PETco_2$ monitoring during exercise is most valuable when *combined* with $Paco_2$ measurements or when combined with more comprehensive measurements of exercise gas exchange.

Sleep studies. For CO_2 monitoring, the use of alveolar gas sampling techniques are limited because the closed system (tight-fitting mask) is poorly tolerated by most sleeping subjects (8). Nasal cannula and pharyngeal catheter sampling for $PETco_2$ is usually complicated by entrainment of room air by these sampling devices, which limits this measurement as a true indicator of alveolar CO_2. Shore and coworkers (143) were unable to obtain reliable end-tidal data in many of their sleeping subjects. End-tidal CO_2 sampling does not accurately reflect $Paco_2$ during nasal continuous positive airway pressure (NCPAP). The widened (PET − Pa)CO_2 gradient probably results from the washout of expired air by NCPAP mask leak. Mouth breathing and hypoventilation also precluded end-tidal CO_2 identification in some patients studied by Naifeh and associates (113). Nonetheless, the majority of subjects who did show end-tidal CO_2 expiratory plateaus demonstrated $Ptcco_2$ to $PETco_2$ differences of 2.3 mm Hg with a correlation coefficient (r) of 0.90 to 0.96. They concluded that end-tidal CO_2 monitoring could reliably reflect $Ptcco_2$ values when end-tidal CO_2 plateaus were selectively sampled.

Summary and Future Direction

This review has summarized the technical requirements and clinical applicability of noninvasive devices for the assessment of oxygenation and alveolar ventilation in infants and adults. The recommendations are summarized according to clinical use in table 2. The limitations of pulse oximetry primarily relate to measurement uncertainties caused by incorporation of the signal from nonarterial sources. The relative contribution of such noise increases with decreasing pulsatile signal strength, which in turn is associated with the state of the microvasculature. The recognition that central sampling sites can be significantly less subject to vasoconstrictive influences than more peripheral sites (144) has generated interest in developing an alternative pulse oximeter technology that can be less site restrictive.

Reflective pulse oximetry technology permits pulse oximetry to be applied to sites other than the ear or finger. Reflection pulse oximetry differs from transmission pulse oximetry primarily in that it uses its output signal light, which is back-scattered by red cells. In such a technology, light scattering is a requirement rather than a computational nuisance. As demonstrated by Mendelson and colleagues (145), the reflection waveforms at the forehead site are sufficiently similar to the transmission waveforms at the finger site that the hardware from a transmission pulse oximeter can also meet the requirements for a reflection oximeter. These investigators also demonstrated that except for a different calibration curve, the same software could also be used. A recent report of Decker and coworkers (146) demonstrates significant response time advantages offered by application of reflective pulse oximetry monitoring at more central sites, such as the forehead. However, current limitation of reflective Spo_2 appear to be related to a more complex and variable relationship between Spo_2 and Sao_2 and a lower signal-to-noise ratio associated with a lower ratio of reflected pulse amplitude to average strength of the reflected signal. Such limitations, however, can likely be minimized by signal enhancement techniques such as those applied by Clark and associates (147) to standard transmission Spo_2 technology.

TABLE 2

RECOMMENDATIONS OF MONITOR PRINCIPLE ACCORDING TO CLINICAL SPECIALTY*

	Spo_2	$Ptco_2$	$PETco_2$	$Ptcco_2$
Exercise	+	−	+	−
Sleep	++	−	+	+
Critical care				
Adults	+	−	+	+
Pediatrics	++	−	+	++
Neonates	+	++	−	++
Anesthesiology	++	+	++	+

* A double plus (++) indicates an enthusiastic recommendation, a single plus (+) indicates a more modest recommendation, and a minus (−) indicates too little clinical utility to support a recommendation.

Improved technology is also required for convenient noninvasive monitoring of $Paco_2$. This is especially true for exercise testing when a noninvasive technique is desirable. In other clinical applications, particularly those in which the patient is intubated, $PETco_2$ is preferred to $Ptcco_2$ because of its greater convenience and better frequency response. The major drawback to $PETco_2$ as an indicator of $Paco_2$ is its sensitivity to abnormalities in the distribution of $\dot{V}/\dot{Q}$.

Future direction for noninvasive $Paco_2$ monitoring are suggested by (*1*) Wagner and associates (148), who demonstrated that blood gas tensions can be predicted from measurements of expired physiologic gas tensions coupled with knowledge of the $\dot{V}/\dot{Q}$ distribution, and (*2*) Yang, who is developing a noninvasive modification of the Wagner method for measuring a $\dot{V}/\dot{Q}$ distribution suitable for predicting $Paco_2$ from the $PETco_2$ data (unpublished work of Ke-Shieng Yang, supported by the National Institutes of Health). Continuous assessment of $Paco_2$ is presently limited by the requirement of a practical gas analyzer that can provide continuous assessment of low-level breath-inert tracer concentrations (in addition to $PETco_2$). However, gas sensor technology has been subject to increasing refinements so that very low concentrations of parts per million can be detected using compact and practical analyzers. Such devices can be interfaced with airway tubing without incurring significant patient encumbrance. The additional cost of this methodology for monitoring $Paco_2$ would essentially be limited to the cost of the tracer gas analyzer. Practical gas sensors are now under development. Low-cost semiconductor sensors have demonstrated capability for monitoring many inert gases that are used in the multiple inert gas method (149). The clinical applicability of these

devices is yet to be determined, but may offer significant advantages over the transcutaneous and end-tidal monitoring techniques presently used.

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